Medical Drug Clinical Criteria

Subject:	Opdivo Qvantig (nivolumab hyaluronidase-nvhy)		
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Overview

This document addresses the use of Opdivo Qvantig (nivolumab hyaluronidase-nvhy), a programmed death receptor-1 (PD-1) blocking antibody, and hyaluronidase, an endoglycosidase. Opdivo Qvantig may be substituted for intravenous nivolumab. The package insert notes Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) is not indicated in combination with ipilimumab.

The following are the FDA indications for Opdivo Qvantig.

Renal Cell Carcinoma

- in those with intermediate or poor risk advanced RCC, as a first-line treatment following combination treatment with intravenous nivolumab and ipilimumab.
- In those with advanced RCC, as a first-line treatment in combination with cabozantinib.
- In those with advanced RCC who have received prior anti-angiogenic therapy.

Melanoma

- In those with unresectable or metastatic melanoma.
- In those with unresectable or metastatic melanoma following combination treatment with intravenous nivolumab and ipilimumab.
- For the adjuvant treatment in those with completely resected stage IIB, stage IIC, Stage III, or Stage IV melanoma.

Non-Small Cell Lung Cancer (NSCLC)

- In those with resectable (tumors ≥ 4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy.
- In those with resectable (tumors ≥4 cm or node positive) NSCLC and no known EGFR mutations or ALK rearrangements, for neoadjuvant treatment, in combination with platinum-doublet chemotherapy, followed by OPDIVO Qvantig monotherapy as adjuvant treatment after surgery.
- In those with metastatic NSCLC and progression on or after platinum based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO Qvantig.

Squamous Cell Carcinoma of the Head and Neck

- In those with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy

Urothelial Carcinoma

- Adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC
- In those with unresectable or metastatic urothelial carcinoma, as first-line treatment in combination with cisplatin and gemcitabine
- In those with locally advanced or metastatic UC who:
    - have disease progression during or following platinum-containing chemotherapy.
    - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-

containing chemotherapy.

Colorectal Cancer

- adult patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy or as monotherapy following combination treatment with intravenous nivolumab and ipilimumab.

Hepatocellular Carcinoma

- In those with HCC previously treated with sorafenib and following combination treatment with intravenous nivolumab and ipilimumab
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Esophageal Squamous Cell Carcinoma (ESCC)

- In those with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT).
- In those with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy
- adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidineand platinum-based chemotherapy

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

- In those with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

The following are current off-label recommendations from NCCN Compendia and Clinical Practice Guideline (CPG).

Updates are currently in progress to all the guidelines. Opdivo Qvantig may be substituted for intravenous nivolumab. Opdivo Qvantig is not indicated in combination with ipilimumab (Yervoy). Where Opdivo has a NCCN 1 or 2A recommendation for use as monotherapy or in combination with chemotherapy, Opdivo Qvantig may be substituted.

- Ampullary Adenocarcinoma
  - Opdivo (2A) monotherapy post IV Opdivo + Yervoy
- Bladder Cancers
  - Opdivo (1, 2A) recommendation as a single agent
- Colon Cancer
  - Opdivo (2A) recommendation as a single agent
- CLL/SLL
  - Opdivo (2A) recommendation as a single agent or in combination with ibrutinib
- Head and Neck Cancer
  - Opdivo (1, 2A) recommendation as a single agent
- Hepatocellular Cancer
  - Opdivo (2A) recommendation as a single agent
- Kaposi Sarcoma
  - Opdivo (2A) recommendation as a single agent
- Kidney Cancer
  - Opdivo (2A) recommendation as a single agent
- Merkel Cell Carcinoma
  - Opdivo (2A) recommendation as a single agent
- Mesothelioma-Pleura and Peritoneal
  - Opdivo (2A) recommendation as a single agent
- Non-small Cell Lung Cancers
  - Opdivo (1, 2A) recommendation as a single agent
- Rectal Cancer
  - Opdivo (2A) recommendation as a single agent
- Small Bowel Adenocarcinoma
  - Opdivo (2A) recommendation as a single agent
- Small Cell Lung Cancer
  - FDA removed indication with Opdivo
- Thyroid Carcinoma-Anaplastic
  - Opdivo (2A) recommendation as a single agent

Other Uses

NCCN Compendia and Clinical Practice Guideline (CPG) also provides the following 2A recommendations for the use of Opdivo Qvantig. However, these recommendations are 2B with Opdivo.

- Anal carcinoma
  - Opdivo (2B) recommendation as a single agent
- Biliary Tract Cancers
  - Opdivo (2B) recommendation as a single agent
- Neuroendocrine Tumors
  - Opdivo (2B) recommendation

Definitions and Measures

Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.

BRAF: The oncogene which directions production of a protein in the regulating MAP kinase/ERKs signaling pathway, which affects cell division, differentiation, and secretion.
Colon cancer: Cancer originating in the tissues of the colon (the longest part of the large intestine). Most colon cancers are adenocarcinomas that begin in cells that make and release mucus and other fluids.
Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).
ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- 0 = Fully active, able to carry on all pre-disease performance without restriction
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 = Dead

Immune checkpoint inhibitor: A type of drug that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. When these proteins are blocked, the "brakes" on the immune system are released and T cells are able to kill cancer cells better. Examples of checkpoint proteins found on T cells or cancer cells include programmed death (PD)-1, PD-ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen (CTLA)-4/B7-1/B7-2.

Karnofsky Performance Status: A scale and criteria used by doctors and researchers to assess an individual's prognosis, measure changes in their function and abilities, and determine their ability to tolerate therapies. The lower the score (from 0-100), the worse the likelihood of survival.

- 100 = Normal, no complaints
- 90 = Able to carry on normal activities
- 80 = Normal activity with effort
- 70 = Care for self. Unable to carry on normal activity or to do active work
- 60 = Requires occasional assistance, but able to care for most of his needs
- 50 = Requires considerable assistance and frequent medical care
- 40 = Disabled. Requires special care and assistance
- 30 = Severely disabled. Hospitalization indicated though death nonimminent
- 20 = Very sick. Hospitalization necessary. Active supportive treatment necessary
- 10 = Moribund
- 0 = Dead

Line of Therapy:

- First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
- Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
- Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.

Melanoma: A type of cancer that begins in the melanocytes. Melanoma is also referred to as malignant melanoma and cutaneous melanoma.

Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

Monoclonal antibody: A protein developed in the laboratory that can locate and bind to specific substances in the body and on the surface of cancer cells.

Mutation: A permanent, transmissible change in genetic material.

Neoadjuvant therapy: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.

Non-small cell lung cancer: A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.

Primary treatment: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. Also called first-line therapy, induction therapy, and primary therapy.

Programmed death (PD)-1 proteins: PD-1 proteins are found on T-cells and attach to PD ligands (PD-L1) found on normal (and cancer) cells (see immune checkpoint inhibitor above). Normally, this process keeps T-cells from attacking other cells in the body. However, this can also prevent T-cells from attacking cancer cells in the body. Examples of FDA approved anti-PD-1 agents include Keytruda (pembrolizumab), Opdivo (nivolumab), and Libtayo (cemiplimab).

Programmed death ligand (PD-L)-1: The ligands found on normal (and cancer) cells to which the PD-1 proteins attach (see immune checkpoint inhibitor above). Cancer cells can have large amounts of PD-L1 on their surface, which helps them to avoid immune attacks. Examples of FDA approved anti-PD-L1 agents include Bavencio (avelumab), Tecentriq (atezolizumab), and Imfinzi (durvalumab).

Progression free survival (PFS): The length of time during and after treatment that an individual lives but does not get worse (usually measured by the size of a tumor or amount of cancer in the body).

Progressive Disease (PD): Cancer that is growing, spreading, or getting worse.

Rectal cancer: Cancer originating in tissues of the rectum (the last several inches of the large intestine closest to the anus).

Refractory Disease: Illness or disease that does not respond to treatment.

Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Unresectable: Unable to be removed with surgery.

Urothelial carcinoma: A type of bladder cancer which occurs in the urinary tract system.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

I. Individual has a diagnosis of Anal carcinoma (NCCN 2A); **AND**
- A. Individual is using as second-line and subsequent therapy; **AND**
- B. Individual is using in metastatic disease; **AND**
- C. Individual is using as a single agent; **AND**
- D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
- E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

II. Individual has a diagnosis of Cervical Cancer (NCCN 2A); **AND**
- A. Individual is using as a single agent; **AND**
- B. Individual is using for second-line or subsequent therapy; **AND**
- C. Individual has CPS ≥ 1 for local/regional recurrence or stage IVB or recurrence with distant metastases; **AND**
- D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
- E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

III. Individual has a diagnosis of Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia (CLL/SLL) (NCCN 2A); **AND**
- A. Individual is using as a single agent or in combination with ibrutinib; **AND**
- B. Individual is using for histologic (Richter) transformation to diffuse large B-cell lymphoma; **AND**
- C. Meets one of the following:
  1. Individual has del (17p)/TP53 mutation; **OR**
  2. Individual is chemotherapy refractory or unable to receive chemoimmunotherapy;

AND

IV. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**

V. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VI. Individual has a diagnosis of Colorectal Cancer, including advanced Appendiceal Adenocarcinoma (NCCN 2A); **AND**
- A. Individual is using as monotherapy; **AND**
- B. Meets one of the following;
  1. Individual has resectable disease for neoadjuvant or initial treatment (NCCN 2A); **AND**
  2. Individual has deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation) (NCCN 2A);

  OR

  3. Individual is using as neoadjuvant therapy in clinical T4b disease (NCCN 2A); **AND**
  4. Individual has deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H];

AND
- C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
- D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VII. Individual has a diagnosis of Colorectal Cancer (Label, NCCN 2A); **AND**
- A. Individual is using as monotherapy in metastatic disease with either defective mismatch repair (dMMR) or high microsatellite instability (MSI-H) mutation, that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan;
- B. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

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OR

VIII. Individual has a diagnosis of Endometrial carcinoma (NCCN 2A); **AND**

A. Individual has a diagnosis of recurrent MSI-H/ or dMMR disease; **AND**
B. Individual is using as a single agent; **AND**
C. Individual is using as second-line or subsequent therapy; **AND**
D. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

IX. Individual has Esophageal and Esophagogastric junction cancer (NCCN 1, 2A); **AND**

A. Individual is using for induction systemic therapy; **AND**
B. Individual is using to relieve dysphagia; **AND**
C. Individual is medically fit and planned for esophagectomy; **AND**
D. Meets one of the following:
    1. Using in combination with platinum-containing chemotherapy and capecitabine or fluorouracil; **OR**
    2. Using as monotherapy, following prior use of intravenous Opdivo in combination with ipilimumab or platinum-containing chemotherapy;

AND

E. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

X. Individual has a diagnosis of unresectable locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC)(Label, NCCN 1, 2A); **AND**

A. Individual is using in combination with fluoropyrimidine- and platinum-containing chemotherapy; **AND**
B. Individual is using as first-line treatment; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XI. Individual has a diagnosis of unresectable locally advanced, recurrent, or metastatic Esophageal Squamous Cell Carcinoma (ESCC)(Label, NCCN 2A); **AND**

A. Individual is using as single agent for second line or subsequent therapy; **AND**
B. Individual has confirmation of disease progression on or had intolerance to fluoropyrimidine- and platinum-based chemotherapy; **AND**
C. Individual has a current ECOG performance status of 0-2 or Karnofsky performance score of 60-100; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XII. Individual has a diagnosis of *completely resected* Esophageal and Esophagogastric Junction Cancers (Label, NCCN 1); **AND**

A. Individual is using as single agent for residual pathologic disease; **AND**
B. Individual has received neoadjuvant chemoradiotherapy (CRT); **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

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XIII. Individual has a diagnosis of Gastric or Esophageal and Esophagogastric Junction Cancers and has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor (NCCN 1, 2A); **AND**

A. Individual is using as a single agent for adenocarcinoma as postoperative management following completely resected disease in those who received preoperative therapy with intravenous nivolumab + ipilimumab; **AND**

B. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIV. Individual has a diagnosis of advanced or metastatic Gastric or Esophageal and Esophagogastric Junction Cancers (Label); **AND**

A. Individual is using in combination with fluoropyrimidine and platinum-containing chemotherapy; **AND**

B. Individual has HER2 negative disease; **AND**

C. Individual has a current ECOG performance status of 0-2; **AND**

D. Individual has no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor; **AND**

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XV. Individual has a diagnosis of Gastric or Esophageal and Esophagogastric Junction Cancers; **AND**

A. Individual is using for palliative care (NCCN 1, 2A); **AND**

B. Individual is not a surgical candidate OR has unresectable locally advanced, recurrent, or metastatic disease;
AND

C. Meets one of the following:

1. Has MSI-H/dMMR tumors; **AND**
2. Using as first-line therapy in combination with fluoropyrimidine- and oxaliplatin;

OR

3. Has Squamous cell carcinoma; **AND**
4. Using as first-line therapy in combination with fluoropyrimide- and platinum-containing chemotherapy;

OR

5. Using as second-line or subsequent therapy as a single agent;

AND

D. Individual has a current ECOG performance status of 0-2 or Karnofsky performance score of 60-100;
AND

E. Individual has no prior checkpoint inhibitor therapy or does not have prior no tumor progression while on therapy with a checkpoint inhibitor; **AND**

F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVI. Individual has a diagnosis of Gastric Cancer (NCCN 1, 2A); **AND**

A. Individual is medically fit for surgery but with surgically unresectable disease; **AND**

1. Has MSI-H or dMMR tumors; **AND**
2. Individual is using in combination with fluoropyrimidine and oxaliplatin;

AND

B. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVII. Individual has a diagnosis of multi-agent chemotherapy-resistant gestational trophoblastic neoplasia (NCCN 2A); **AND**

A. Individual has recurrent or progressive intermediate trophoblastic tumor or high-risk disease; **AND**

B. Individual is using as single-agent therapy; **AND**

C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**

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D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVIII. Individual has a diagnosis of advanced Hepatocellular Carcinoma (Label, NCCN 2A); **AND**

A. Individual is using as a single agent in those classified as Child-Pugh Class B; **AND**
B. Individual has a current ECOG performance status of 0-2; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIX. Individual has a diagnosis of Hodgkin Lymphoma (Label, NCCN 1, 2A); **AND**

A. Individual is using for relapsed or refractory Hodgkin lymphoma except for those with lymphocyte-predominant Hodgkin lymphoma; **AND**
   1. Using in one of the following ways:
      a. Individual is as a single agent; **OR**
      b. Individual is using in combination with brentuximab vedotin or with ifosfamide, carboplatin, etoposide (ICE) as primary systemic therapy or second-line therapy;

   OR

B. Individual is using in combination with AVD (doxorubicin, vinblastine, dacarbazine) for primary treatment;

AND

C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XX. Individual has a diagnosis of Pediatric Classic Hodgkin Lymphoma (NCCN 2A):

A. Individual is using for relapsed or refractory Hodgkin lymphoma except for those with lymphocyte-predominant Hodgkin lymphoma; **AND**
B. Using in one of the following ways:
   1. Individual is as a single agent; **OR**
   2. Individual is using in combination with brentuximab vedotin;

AND

C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXI. Individual has a diagnosis of relapsed/refractory advanced classic Kaposi Sarcoma (NCCN 2A); **AND**

A. Individual is using as a single agent; **AND**
B. Individual is using as subsequent systemic therapy; **AND**
C. Individual does not have multicentric Castleman Disease (MCD) or KSHV-associated inflammatory cytokine syndrome (KICS);

OR

XXII. Individual has a diagnosis of Malignant Pleural or Peritoneal Mesothelioma (NCCN 2A); **AND**

A. Individual is using as a single agent for subsequent therapy; **AND**
B. Individual has a ECOG performance status of 0-2; **AND**
C. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIII. Individual has a diagnosis of Melanoma (Cutaneous or Uveal); **AND**

A. Individual has unresectable or metastatic melanoma (Label, NCCN 1, 2A); **AND**
   1. Individual is using as a single agent; **AND**
   2. Current ECOG performance status of 0-2; **AND**
   3. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

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B. Individual has resected advanced melanoma (Label, NCCN 1, 2A); **AND**
1. Individual is using as a single agent for adjuvant therapy; **AND**
2. Individual has resected stage IIB, stage IIC, stage III, or stage IV disease; **AND**
3. Current ECOG performance status of 0-2; **AND**
4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIV. Individual has a diagnosis of metastatic Melanoma with brain metastases and the following criteria are met (NCCN 2A); **AND**

A. Individual has a primary diagnosis of melanoma; **AND**
B. Using in one of the following ways:
1. Individual has asymptomatic brain metastases (Long 2017, 2018, Tawbi 2017);
OR
2. Individual has BRAF non-specific asymptomatic brain metastases; **AND**
3. Individual is using as monotherapy;

AND

C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXV. Individual has a diagnosis of Merkel Cell Carcinoma (Label, NCCN 2A); **AND**

A. Individual is using as a single agent; **AND**
B. Individual has presence of metastatic or recurrent locoregional MCC determined to be not amenable to definitive surgery or radiation therapy; **AND**
C. Current ECOG performance status of 0-2; **AND**
D. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

F. Individual is using as a single agent (NCCN 2A); **AND**
G. Individual has M1 disseminated disease if anti-PD-L1 or anti-PD-1 therapy is contraindicated or disease has progressed on anti-PD-L1 or anti-PD-1 monotherapy; **AND**
H. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXVI. Individual has a diagnosis of Non-Small Cell Lung Cancer (NSCLC) (Label, NCCN 1, 2A); **AND**

A. Individual has recurrent, advanced, or metastatic NSCLC; **AND**
1. Individual is using as a single agent; **AND**
2. Confirmation of disease progression on or after platinum-containing chemotherapy; **AND**
3. Current ECOG performance status of 0-2; **AND**
4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
5. Individual is not receiving therapy for an autoimmune disease, chronic condition, or interstitial lung disease with a systemic immunosuppressant;

OR

B. Individual has resectable NSCLC and using as neoadjuvant therapy (Label, NCCN 2A); **AND**
1. Individual is using in combination with platinum-doublet chemotherapy (e.g. paclitaxel and carboplatin); **AND**
2. Resectable is defined as tumors ≥ 4 cm or node positive; **AND**
3. Individual has no know EGFR mutations or ALK rearrangements; **AND**
4. Individual continues with Opdivo as a single agent for adjuvant treatment after surgery; **AND**
5. Current ECOG performance status of 0-2; **AND**
6. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
7. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

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OR

XXVII. Individual has a diagnosis of metastatic NSCLC with brain metastases (NCCN 2A); **AND**

A. Individual has a primary diagnosis of non-small cell lung cancer; **AND**
B. Individual is using as single agent for brain metastases; **AND**
C. Individual has PD-L1 expression positive (≥ 1%) tumors; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXVIII. Individual has a diagnosis of Primary Mediastinal Large B-Cell Lymphoma (NCCN 2A); **AND**

A. Individual is using for pediatric aggressive mature B-cell lymphoma; **AND**
   1. Individual is using for relapsed or refractory disease as a single agent; **OR**
   2. Individual is using for consolidation/additional therapy in combination with brentuximab vedotin after partial response achieved after therapy for relapsed or refractory disease;

AND

B. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIX. Individual has a diagnosis of Renal Cell Carcinoma (RCC) (Label, NCCN 2A); **AND**

A. Individual has advanced or metastatic RCC ; **AND**
   1. Individual is using as monotherapy; **AND**
   2. Histological confirmation of RCC with clear-cell component; **AND**
   3. Individual has confirmation of disease progression after one or two prior anti-angiogenic regimens (e.g. axitinib, bevacizumab [or its biosimilar], pazopanib, sorafenib, sunitinib, etc.) for treatment of advanced or metastatic disease; **AND**
   4. Current ECOG performance status of 0-2; **AND**
   5. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   6. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant

OR

B. Individual has relapsed, recurrent, or advanced RCC (Label, NCCN 1, 2A); **AND**
   1. Individual is using as first-line therapy or subsequent therapy in combination with cabozantinib tablets; **AND**
   2. Current ECOG performance status of 0-2; **AND**
   3. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

C. Individual has relapsed, recurrent, or advanced RCC (NCCN 2A); **AND**
   1. Individual is using as subsequent therapy in combination with cabozantinib; **AND**
   2. Individual has a current ECOG performance status of 0-2; **AND**
      3. Individual has had prior immune-oncology therapy (e.g. pembrolizumab); **AND**
      4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

D. Individual has relapse or metastatic non-clear cell RCC (nccRCC) [including hereditary leiomyomatosis and renal cell carcinoma (HLRCC)] (NCCN 2A); **AND**
   1. Individual is using as systemic therapy as a single agent or in combination with cabozantinib; **AND**
   2. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   3. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXX. Individual has a diagnosis of Small Bowel Adenocarcinoma (SBA) ~~including Ampullary adenocarcinoma~~ (NCCN 2A); **AND**

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A. Individual has advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation); **AND**
B. Individual is using as monotherapy; **AND**
C. Current ECOG performance status of 0-2; **AND**
D. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXI. Individual has a diagnosis of Extranodal NK/T-cell lymphomas (NCCN 2A); **AND**
A. Individual has relapsed/refractory disease; **AND**
B. Individual is using Opdivo as monotherapy following alternate combination chemotherapy not previously used (e.g.~~with~~ asparaginase-based regimen); **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual has a current ECOG performance status of 0-2; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXII. Individual has a diagnosis of Squamous Cell Carcinoma of the Head and Neck (SCCHN (Label, NCCN 1):
A. Individual has recurrent, unresectable, or metastatic SCCHN; **AND**
1. Individual is using as monotherapy; **AND**
2. Individual has confirmation of disease progression on or after platinum-containing chemotherapy; **OR**
3. Individual is using in combination with cetuximab (NCCN 2A); **AND**
4. Individual is using for first-and subsequent line therapy;

AND
5. Current ECOG performance status of 0-2; **AND**
6. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
7. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXIII. Individual has a diagnosis of Head and Neck cancers (NCCN 1, 2A); **AND**
A. Using for one of the following types of cancers:
1. Individual has recurrent, unresectable, oligometastatic, or metastatic Nasopharyngeal Cancers (NCCN 2A); **AND**
2. Individual has no surgery or radiotherapy (RT) options; **AND**
a. Individual is using nivolumab in combination with cisplatin and gemcitabine; ~~**OR**~~
AND
3. Has not received another anti-PD-1 or anti-PD-L1 agent;

OR

XXXIV. Individual has metastatic Anaplastic Thyroid carcinoma (NCCN 2A); **AND**
A. Individual is using as a single agent; **AND**
B. Current ECOG performance status of 0-2; **AND**
C. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXV. Individual has Urothelial carcinoma (Label, NCCN 1, 2A): **AND**
A. Individual has locally advanced, recurrent, or metastatic disease; **AND**
1. Individual is using as a single agent; **AND**
2. Individual meets one of the following criteria:
a. Confirmation of disease progression on or after platinum-containing or other chemotherapy; **OR**
b. Confirmation of disease progression within 12 months of receiving neoadjuvant or adjuvant treatment with platinum-containing chemotherapy;

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OR

3. Individual is using as single agent for adjuvant therapy; **AND**
4. Individual is at high risk of recurrence after having radical resection;

AND

B. Current ECOG performance status of 0-2; **AND**
C. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXVI. Individual has urothelial carcinoma (Label, NCCN 1, 2A); **AND**

A. Individual has unresectable, recurrent, or metastatic disease; **AND**
B. Individual is using in combination with cisplatin and gemcitabine; **AND**
C. Individual is using as first-line treatment; **AND**
D. Current ECOG performance status of 0-2; **AND**
E. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXVII. Individual has a diagnosis of Urothelial Carcinoma of the Prostate (NCCN 2A); **AND**

A. Individual is using as adjuvant therapy; **AND**
B. Individual is using for tumors with stromal invasion if platinum-based neoadjuvant chemotherapy not given and pT3, pT4a, pN+; **AND**
C. Individual is using as a single agent;

OR

XXXVIII. Individual has a diagnosis of Central Nervous System Cancers- Pediatric Diffuse High-Grade Gliomas (NCCN 2A); **AND**

A. Individual is using as single agent for hypermutant tumor; **AND**
B. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXIX. Individual has a diagnosis of recurrent or metastatic Vaginal Cancer (NCCN 2A); **AND**

A. Individua is using a single agent; **AND**
B. Individual is using as second-line or subsequent therapy; **AND**
C. Individual has PD-L1 expression positive (CPS ≥ 1%) tumor; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XL. Individual has a diagnosis of advanced or recurrent/ ~~or~~ metastatic Vulvar Cancer (NCCN 2A); **AND**

A. Individual is using as a single agent; **AND**
B. Individual is using as second-line or subsequent therapy; **AND**
C. Individual has HPV-related tumor; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

~~I. Individual has a diagnosis of Anal carcinoma (NCCN 2A); **AND**~~
~~A. Individual is using as second-line and subsequent therapy; **AND**~~
~~B. Individual is using in metastatic disease; **AND**~~
~~C. Individual is using as a single agent; **AND**~~
~~D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**~~
~~E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;~~

~~**OR**~~

~~II. Individual has a diagnosis of Cervical Cancer (NCCN 2A); **AND**~~
~~A. Individual is using as a single agent; **AND**~~
~~B. Individual is using for second-line or subsequent therapy; **AND**~~

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C. Individual has CPS ≥ 1 for local/regional recurrence or stage IVB or recurrence with distant metastases; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

III. Individual has a diagnosis of Colorectal Cancer, including advanced Appendiceal Adenocarcinoma (Label, NCCN 2A); **AND**
A. Individual meets one of the following criteria:
i. Individual is using as monotherapy in primary treatment for unresectable metachronous metastases (defective mismatch repair/ high microsatellite instability [dMMR/MSIH] only) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; **OR**
ii. Individual is using as monotherapy as subsequent therapy for unresectable advanced or metastatic disease (defective mismatch repair/ high microsatellite instability [dMMR/MSIH] only) following previous treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan- based chemotherapy (Label, NCCN 2A); **AND**
B. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

IV. Individual has a diagnosis of unresectable locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) (Label, NCCN 2A); **AND**
A. Individual is using in combination with fluoropyrimidine- and platinum-containing chemotherapy; **AND**
B. Individual is using as first-line treatment; **AND**
C. Individual has a current ECOG performance status of 0-1; **AND**
D. Individual has not received prior treatment with anti-PD-1, anti-PD-L1, any antibody or drug specifically targeting T-cell co-stimulation, or checkpoint pathways; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

V. Individual has a diagnosis of unresectable locally advanced, recurrent, or metastatic Esophageal Squamous Cell Carcinoma (ESCC) (Label, NCCN 1, 2A); **AND**
A. Individual is using as single agent for second line or subsequent therapy; **AND**
B. Individual has confirmation of disease progression on or had intolerance to fluoropyrimidine- and platinum-based chemotherapy; **AND**
C. Individual has a current ECOG performance status of 0-2 or Karnofsky performance score of 60-100; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VI. Individual has a diagnosis of *completely resected* Esophageal and Esophagogastric Junction Cancers (Label, NCCN 1); **AND**
A. Individual is using as single agent for residual pathologic disease; **AND**
B. Individual has received neoadjuvant chemoradiotherapy (CRT); **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VII. Individual has a diagnosis of Gastric or Esophageal and Esophagogastric Junction Cancers and has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor (NCCN 2A); **AND**

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A. Individual is using as a single agent for adenocarcinoma as postoperative management following completely resected disease in those who received preoperative therapy with intravenous nivolumab + intravenous ipilimumab; **AND**
B. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VIII. Individual has a diagnosis of advanced or metastatic Gastric, or Esophageal and Esophagogastric Junction Cancers (Label, NCCN 1, 2A); **AND**
A. Individual is using in combination with fluoropyrimidine and platinum-containing chemotherapy; **AND**
B. Individual has HER2 negative disease; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

IX. Individual has a diagnosis of unresectable locally advanced, recurrent or metastatic Gastric or Esophageal and Esophagogastric Junction Cancers (NCCN 2A); **AND**
A. Individual has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor; **AND**
B. Individual has a current ECOG performance status of 0-2 or Karnofsky performance score of 60-100; **AND**
C. Using in combination with fluoropyrimidine- and platinum-based chemotherapy; **AND**
D. Individual has not received another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

X. Individual has a diagnosis of multi-agent chemotherapy-resistant gestational trophoblastic neoplasia; **AND**
A. Individual has intermediate or high-risk disease; **AND**
B. Individual is using as single-agent therapy; **AND**
C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XI. Individual has a diagnosis of advanced Hepatocellular Carcinoma (Label, NCCN 2A); **AND**
A. Individual is using as a single agent in those classified as Child-Pugh Class B; **AND**
B. Individual has a current ECOG performance status of 0-2; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XII. Individual has a diagnosis of Hodgkin Lymphoma (Label, NCCN 2A); **AND**
A. Individual is using for relapsed or refractory Hodgkin lymphoma except for those with lymphocyte-predominant Hodgkin lymphoma; **AND**
B. Individual is as a single agent; **OR**
C. Individual is using in combination with brentuximab vedotin or with ifosfamide, carboplatin, etoposide (ICE); **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIII. Individual has a diagnosis of relapsed/refractory advanced classic Kaposi Sarcoma and the following criteria are met (NCCN 2A):
A. Individual is using as subsequent systemic therapy; **AND**
B. Individual does not have multicentric Castleman Disease (MCD) or KSHV-associated inflammatory cytokine syndrome (KICS);

OR

XIV. Individual has a diagnosis of Malignant Pleural or Peritoneal Mesothelioma (NCCN 2A); **AND**

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A. Individual is using as a single agent for subsequent therapy; **AND**
B. Individual has a ECOG performance status of 0-2; **AND**
C. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XV. Individual has a diagnosis of Melanoma (Cutaneous or Uveal) and the following criteria are met (Label, NCCN 1):
A. Individual has unresectable or metastatic melanoma; **AND**
1. Individual is using as a single agent; **AND**
2. Current ECOG performance status of 0-2; **AND**
3. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

B. Individual has resected advanced melanoma and the following criteria are met (Label, NCCN 1, 2A); **AND**
1. Individual is using as a single agent for adjuvant therapy; **AND**
2. Individual has resected stage IIB, stage IIC, stage III, or stage IV disease; **AND**
3. Current ECOG performance status of 0-2; **AND**
4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

C. Individual has Melanoma (Cutaneous or Uveal) (Label); **AND**
1. One of the following:
a. Individual has melanoma with involvement of lymph nodes; **OR**
b. Individual has metastatic melanoma and has undergone complete resection;

AND

2. Individual is using as a single agent for adjuvant therapy;

OR

D. Individual has metastatic or unresectable melanoma (Cutaneous or Uveal) (NCCN 2A); **AND**
1. Individual is using as second-line or subsequent systemic therapy; **AND**
2. Using as a single agent if disease control occurred with prior anti-PD-1 immunotherapy as re-induction therapy;

OR

XVI. Individual has a diagnosis of metastatic Melanoma with brain metastases and the following criteria are met (NCCN 2A):
A. Individual has a primary diagnosis of melanoma; **AND**
B. Individual has asymptomatic brain metastases (Long 2017, 2018, Tawbi 2017);**AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVII. Individual has a diagnosis of Merkel Cell Carcinoma and the following criteria are met (Label, NCCN 2A):
A. Individual is using as a single agent; **AND**
B. Individual has presence of metastatic or recurrent locoregional MCC determined to be not amenable to definitive surgery or radiation therapy; **AND**
C. Current ECOG performance status of 0-2; **AND**
D. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;
OR
F. Individual is using as a single agent (NCCN 2A); **AND**
G. Individual has M1 disseminated disease if anti-PD-L1 or anti-PD-1 therapy is contraindicated or disease has progressed on anti-PD-L1 or anti-PD-1 monotherapy; **AND**
H. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

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OR

XVIII. Individual has a diagnosis of Non-Small Cell Lung Cancer (NSCLC) and the following criteria are met (Label, NCCN 1, 2A):

A. Individual has metastatic NSCLC; **AND**

1. Individual is using as a single agent; **AND**
2. Confirmation of disease progression on or after platinum-containing chemotherapy; **AND**
3. Current ECOG performance status of 0-2; **AND**
4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
5. Individual is not receiving therapy for an autoimmune disease, chronic condition, or interstitial lung disease with a systemic immunosuppressant;

OR

B. Individual has resectable NSCLC and using as neoadjuvant therapy (Label, NCCN 2A); **AND**

1. Individual is using in combination with platinum-doublet chemotherapy (e.g. paclitaxel and carboplatin); **AND**
2. Resectable is defined as tumors ≥ 4 cm or node positive; **AND**
3. Current ECOG performance status of 0-2; **AND**
4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

C. Individual has resectable NSCLC (Label); **AND**

1. Resectable is defined as tumors ≥ 4 cm and/or node positive; **AND**
2. Individual has no known EGFR mutations or ALK rearrangements; **AND**
3. Using as adjuvant therapy post-surgery; **AND**
4. Individual is using as a single agent after prior combination use of Opdivo or Opdivo Qvantig and platinum-doublet chemotherapy; **AND**
5. Current ECOG performance status of 0-2; **AND**
6. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
7. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

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OR

XIX. Individual has a diagnosis of metastatic NSCLC with brain metastases and the following criteria are met (NCCN 2A):

A. Individual has a primary diagnosis of non-small cell lung cancer; **AND**

B. Individual is using as single agent for brain metastases; **AND**

C. Individual has PD-L1 expression positive (≥ 1%) tumors; **AND**

D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XX. Individual has a diagnosis of Renal Cell Carcinoma (RCC) (Label, NCCN 2A); **AND**

A. Individual has advanced or metastatic RCC ; **AND**

1. Individual is using as monotherapy; **AND**
2. Histological confirmation of RCC with clear-cell component; **AND**
3. Individual has confirmation of disease progression after one or two prior anti-angiogenic regimens (e.g. axitinib, bevacizumab [or bevacizumab biosimilar], pazopanib, sorafenib, sunitinib, etc.) for treatment of advanced or metastatic disease; **AND**
4. Current ECOG performance status of 0-2; **AND**
5. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
6. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

B. Individual has relapsed, recurrent, or advanced RCC (Label, NCCN 1, 2A); **AND**

1. Individual is using as first-line therapy or subsequent therapy in combination with cabozantinib tablets; **AND**
2. Current ECOG performance status of 0-2; **AND**

3. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

C. Individual has relapsed, recurrent, or advanced RCC (NCCN 2A); **AND**
5. Individual is using as subsequent therapy in combination with cabozantinib; **AND**
6. Individual has a current ECOG performance status of 0-2; **AND**
7. Individual has had prior immune-oncology therapy (e.g. pembrolizumab); **AND**
8. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

D. Individual has relapse or metastatic non-clear cell RCC (nccRCC) (NCCN 2A); **AND**
2. Individual is using as systemic therapy as a single agent or in combination with cabozantinib; **AND**
3. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXI. Individual has a diagnosis of Small Bowel Adenocarcinoma (SBA) including Ampullary Adenocarcinoma and meets the following criteria (NCCN 2A):
A. Individual has advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only); **AND**
B. Individual is using as monotherapy; **AND**
C. Current ECOG performance status of 0-2; **AND**
D. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXII. Individual has a diagnosis of Extranodal NK/T-cell lymphomas (NCCN 2A); **AND**
A. Individual has relapsed/refractory disease; **AND**
B. Individual is using following treatment with asparaginase-based regimen; **AND**
C. Individual is using as monotherapy; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual has a current ECOG performance status of 0-2; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIII. Individual has a diagnosis of advanced or metastatic Soft Tissue Sarcoma and Aggressive Soft Tissue Neoplasms (NCCN 2A); **AND**
A. Individual is using as a single agent; **AND**
B. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIV. Individual has a diagnosis of Squamous Cell Carcinoma of the Head and Neck (SCCHN) and meet the following criteria (Label, NCCN 1):
A. Individual has recurrent, unresectable, or metastatic SCCHN; **AND**
1. Individual is using as monotherapy; **AND**
2. Individual has confirmation of disease progression on or after platinum-containing chemotherapy; **AND**
3. Current ECOG performance status of 0-2; **AND**
4. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXV. Individual has a diagnosis of Head and Neck cancers (NCCN 2A); **AND**
A. Using for one of the following types of cancers:

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1. Individual has recurrent, unresectable, oligometastatic, or metastatic Nasopharyngeal Cancers (INCCN 2A); **AND**
2. Individual has no surgery or radiotherapy (RT) options; **AND**
3. Individual is using in combination with cisplatin and gemcitabine; **AND**
4. Has not received another anti-PD-1 or anti-PD-L1 agent; **OR**

B. Individual has squamous recurrent, unresectable, or metastatic non-nasopharyngeal cancer; **AND**
1. Individual has no surgery or radiotherapy options; **AND**
2. Individual is using in combination with cetuximab;

OR

XXVI. Individual has Urothelial carcinoma and meet the following criteria (Label, NCCN 2A):
A. Individual has locally advanced or metastatic disease; **AND**
1. Individual is using as a single agent; **AND**
2. Individual meets one of the following criteria:
a. Confirmation of disease progression on or after platinum-containing chemotherapy; **OR**
b. Confirmation of disease progression within 12 months of receiving neoadjuvant or adjuvant treatment with platinum-containing chemotherapy;

OR

B. Individual is using as single agent for adjuvant therapy; **AND**
1. Individual is at high risk of recurrence after having radical resection;

AND

C. Current ECOG performance status of 0-2; **AND**
D. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXVII. Individual has urothelial carcinoma (Label); **AND**
A. Individual has unresectable or metastatic disease; **AND**
B. Individual is using in combination with cisplatin and gemcitabine; **AND**
C. Individual is using as first-line treatment; **AND**
D. Current ECOG performance status of 0-2; **AND**
E. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXVIII. Individual has a diagnosis of Central Nervous System Cancers- Pediatric Diffuse High-Grade Gliomas (NCCN 2A); **AND**
A. Individual is using as single agent for hypermutant tumor; **AND**
B. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIX. Individual has a diagnosis of recurrent or metastatic Vulvar Cancer (NCCN 2A); **AND**
A. Individual is using as a single agent; **AND**
B. Individual is using as second-line or subsequent therapy; **AND**
C. Individual has HPV-related tumor; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

***Note:** Actionable molecular markers include EGFR, ALK, ROS1, BRAF, NTRK, MET, RET, and ERBB2 (HER2) mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NCCN 1, 2A).

Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may not be approved for the following:
I. When Opdivo Qvantig is used in combination with intravenous ipilimumab (Yervoy); **AND**
II. When the above criteria are not met and for all other indications.

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Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

~~C9399~~	~~Unclassified drugs or biologicals [when specified as Opdivo Qvantig (nivolumab and hyaluronidase-nvhy)]~~
~~J9999~~	~~Not otherwise classified, antineoplastic drugs [when specified as Opdivo Qvantig (nivolumab and hyaluronidase-nvhy)]~~
J9289	Injection, nivolumab, 2 mg and hyaluronidase-nvhy [Opdivo Qvantig]

ICD-10 Diagnosis

	~~All diagnosis pend.~~
C00.0-C06.9	Malignant neoplasm of lip, tongue, oral cavity
C09.0-C13.9	Malignant neoplasm of tonsil, oropharynx, nasopharynx, pyriform sinus, hypopharynx
C14.0-C14.9	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
C15.3-C16.9	Malignant neoplasm of esophagus, stomach
C17.0-C20	Malignant neoplasm of small intestine, colon, rectosigmoid junction, rectum
C21.0-C21.9	Malignant neoplasm of anus and anal canal
C22.0	Liver cell carcinoma
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C30.0	Malignant neoplasm of nasal cavity
C31.0-C31.1	Malignant neoplasm of maxillary sinus, ethmoidal sinus
C32.0-C32.9	Malignant neoplasm of larynx
C33	Malignant neoplasm of trachea
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C43.0-C43.9	Malignant melanoma of skin
C44.02	Squamous cell carcinoma of skin of lip
C44.320	Squamous cell carcinoma of skin of unspecified parts of face
C44.42	Squamous cell carcinoma of skin of scalp and neck
C45.0-C45.9	Mesothelioma
C46.0-C46.9	Kaposi's sarcoma
C4A.0-C4A.9	Merkel cell carcinoma
C51.0-C53.9	Malignant neoplasm of vulva, vagina, cervix uteri
C54.0-C55	Malignant neoplasm of corpus uteri, uterus part unspecified
C58	Malignant neoplasm of placenta
C61	Malignant neoplasm of prostate
C64.0-C65.9	Malignant neoplasm of kidney, renal pelvis
C66.0-C68.0	Malignant neoplasm of ureter, bladder, urethra
C69.30-C69.32	Malignant neoplasm of choroid

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C69.40-C69.42	Malignant neoplasm of ciliary body
C71.0-C71.9	Malignant neoplasm of brain
C72.0	Malignant neoplasm of spinal cord
C72.1	Malignant neoplasm of cauda equina
C72.9	Malignant neoplasm of central nervous system, unspecified
C73	Malignant neoplasm of thyroid gland
C76.0	Malignant neoplasm of head, face and neck
C79.31-C79.32	Secondary malignant neoplasm of brain, cerebral meninges
C81.10-C81.99	Hodgkin lymphoma (classical)
C83.00-C83.09	Small cell B-cell lymphoma
C83.30-C83.38	Diffuse large B-cell lymphoma
C83.398	Diffuse large B-cell lymphoma of other extranodal and solid organ sites
C84.Z0-C84.Z9	Other mature T/NK-cell lymphomas
C84.90-C84.99	Mature T/NK-cell lymphomas, unspecified
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
C86.00	Extranodal NK/T-cell lymphoma, nasal type not having achieved remission
C91.10-C91.12	Chronic lymphocytic leukemia of B-cell type
D09.0	Carcinoma in situ of bladder

Document History

Revised: 05/16/2025
Document History:

- 05/16/2025 – Select Review: Align Opdivo updates to Opdivo Qvantig criteria. Add criteria for CLL/SLL. Clarify Colorectal cancer with FDA indication updates. Clarify use in R/R Hodgkin lymphoma and combination use with AVD. Add criteria for use in cetuximab in SCCHN and remove duplicative criteria. Coding Reviewed: Removed HCPCS NOC C9399, J9999 and all diagnosis pend effective 6/30/25. Added HCPCS J9289 effective 7/1/25. Added ICD-10-CM C00.0-C06.9, C09.0-C22.0, C22.8-C30.0, C31.0-C31.1, C32.0-34.92, C43.0-C43.9, C44.02, C44.320, C44.42, C45.0-C46.9, C4A.0-C4A.9, C51.0-C55, C58, C61, C64.0-C68.0, C69.30-C69.32, C69.40-C69.42, C71.0-C72.1, C72.9, C73, C76.0, C79.31-C79.32, C81.10-C81.99, C83.00-C83.09, C83.30-C83.38, C83.398, C84.Z0-C84.Z9, C84.90-C84.99, C85.20-C85.29, C86.00, C91.10-C91.12, D09.0.
- 02/21/2025 – Select Review: Initial review of Opdivo Qvantig (nivolumab-hyaluronidase). Include criteria for Opdivo monotherapy and chemotherapy combination use from NCCN 1, 2A recommendations. Coding Reviewed: Added HCPCS NOC C9399 and J9999 and all diagnosis pend for Opdivo Qvantig.

References

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Updated periodically.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2025; Updated periodically.
4. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. January 14, 2025.
    a. Ampullary adenocarcinoma. V2.2025. Revised January 10, 2025.
    b. Anal Carcinoma. V1.2025. Revised December 4, 2024.
    c. Biliary Tract Cancers. V6.2024. Revised January 10, 2024.
    d. B-Cell Lymphomas. V1.2024. Revised January 18, 2023
    e. Bladder cancer. V5.2024. Revised October 28, 2024.
    f. Bone cancer. V1.2025. Revised August 20, 2024.
    g. Central Nervous System Cancers V3.2024. Revised September 30, 2024.
    h. Cervical Cancer. V1.2025. Revised December 19, 2024.
    i. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V1.2025. Revised October 1, 2024.

j. Colon Cancer V4.2023. Revised November 16, 2023.
k. Cutaneous Melanoma. V1.2025. December 20. 2024.
l. Esophageal and esophagogastric junction cancers. V5.2024. Revised December 20, 2024.
m. Gastric cancer. V5.2024. Revised December 20, 2024.
n. Gestational Trophoblastic Neoplastic. V1.2025. Revised December 17, 2024.
o. Head and neck cancers. V1.2025. Revised November 26, 2024
p. Hepatocellular Carcinoma. V4.2024. Revised January 10, 2025.
q. Hodgkin Lymphoma V1.2024. Revised October 12, 2023.
r. Kaposi Sarcoma. V2.2025. Revised January 14, 2025.
s. Kidney Cancer. V3.2025. Revised January 9, 2025
t. Merkel Cell Carcinoma. V1.2024. Revised November 22, 2023.
u. Malignant Pleural Mesothelioma V2.2025. Revised January 14, 2025.
v. Malignant Peritoneal Mesothelioma. V2.2025. Revised January 14, 2025.
w. Cutaneous Melanoma V3.2023. Revised October 27, 2023.
x. Neuroendocrine and Adrenal Tumors. V1.2023. Revised August 2, 2023.
y. Non-Small Cell Lung Cancer. V3.2025. Revised January 14, 2025.
z. Pediatric Aggressive Mature B-Cell Lymphomas. V2.2024. Revised September 3, 2024.
aa. Pediatric Central Nervous System Cancers. V1.2025. Revised November 8, 2024.
bb. Pediatric Hodgkin Lymphoma. V1.2024. Revised May 14, 2024.
cc. Rectal Cancer V4.2024. Revised August 22, 2024.
dd. Small Bowel Adenocarcinoma. V1.2025. Revised December 4, 2024.
ee. Small cell lung cancer. V4.2025. Revised January 13, 2025.
ff. Soft Tissue Sarcoma. V4.2024. Revised November 21, 2024.
gg. T-Cell Lymphomas. V1.2025. Revised November 11, 2024.
hh. Thyroid Carcinoma. V5.2024. Revised January 15, 2025.
ii. Uterine neoplasms. V1.2025. Revised December 16, 2024.
jj. Vaginal Cancer V3.2025. Revised December 16, 2024.
kk. Uveal Melanoma. V1.2024. Revised May 23, 2024.
ll. Vulvar Cancer. V4.2024. Revised May 1, 2024.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.